Genetically Engineered Mesenchymal Stem Cells as a Proposed Therapeutic for Huntington's Disease.

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Funding Grants: Sustained siRNA production from human MSC to treat Huntingtons Disease and other neurodegenerative disorders, MSC engineered to produce BDNF for the treatment of Huntington's disease

Public Summary:
The review, written with collaborator Dr. Gary Dunbar, discusses studies over the past decade that have used mesenchymal stem cells (MSCs) and MSCs engineered to produce neural growth factors in the brain, for the treatment of Huntington's disease. Some of the therapeutics, such as MSCs engineered to secrete brain-derived neurotrophic factor (MSC/BDNF) have been effective in HD mouse models. This agent has been shown to correct movement disorders and characteristic clasping phenotype in HD mice. MSC implantation into the striata has also been shown to restore striatal volume in HD mice. These studies are reviewed and summarized in table format in the manuscript. The Dunbar and Nolta laboratories are working together, with many national and international collaborators, to bring the proposed therapeutic MSC/BDNF into Phase I clinical trials to treat Huntington's disease. This work is supported by CIRM translational grant TR1-01257 and CIRM disease team planning grant DR2A-05415, "MSC engineered to produce BDNF for the treatment of Huntington's disease."

Scientific Abstract:
There is much interest in the use of mesenchymal stem cells/marrow stromal cells (MSC) to treat neurodegenerative disorders, in particular those that are fatal and difficult to treat, such as Huntington's disease. MSC present a promising tool for cell therapy and are currently being tested in FDA-approved phase I-III clinical trials for many disorders. In preclinical studies of neurodegenerative disorders, MSC have demonstrated efficacy, when used as delivery vehicles for neural growth factors. A number of investigators have examined the potential benefits of innate MSC-secreted trophic support and augmented growth factors to support injured neurons. These include overexpression of brain-derived neurotrophic factor and glial-derived neurotrophic factor, using genetically engineered MSC as a vehicle to deliver the cytokines directly into the microenvironment. Proposed regenerative approaches to neurological diseases using MSC include cell therapies in which cells are delivered via intracerebral or intrathecal injection. Upon transplantation, MSC in the brain promote endogenous neuronal growth, encourage synaptic connection from damaged neurons, decrease apoptosis, reduce levels of free radicals, and regulate inflammation. These abilities are primarily modulated through paracrine actions. Clinical trials for MSC injection into the central nervous system to treat amyotrophic lateral sclerosis, traumatic brain injury, and stroke are currently ongoing. The current data in support of applying MSC-based cellular therapies to the treatment of Huntington's disease is discussed.